Pharmacokinetics and Drug Therapy in Pregnancy and Lactation

Catherine Stika, MD

Conflict of Interest

- I have no financial conflicts of interest
- Some of the medications I will be discussing will include unapproved or off-label indications for medications we use in obstetrics, supported by evidence in the literature but not formally approved by the FDA.
Pregnancy – Special Population

- In the late 1990s the FDA & NIH convened a series of conferences to discuss medication usage in pregnancy
- Pregnancy Labeling change – July 2015
- Pregnancy = Special Population
- FDA Guidance: Conduct of PK Studies in Pregnancy
- First NICHD OPRU funded 2004

Therapeutic Range - Efficacy

![Therapeutic Range Diagram](image)

- **C<sub>max</sub>** (maximum concentration)
- **t<sub>max</sub>** (time to maximum concentration)
- **AUC** (area under the curve)
- **Duration of action**
- **Therapeutic Range**
- **MTC** (maximal therapeutic concentration)
- **MEC** (minimal effective concentration)
Minimum Effective Concentration

Non-pregnant AUC

Pregnant AUC

Once Daily vs Twice Daily Dosing

Duration of action

Therapeutic Range

Onset time $t_{\text{max}}$

Time

$C_{\text{max}}$

AUC

MEC

MTC
Drug Therapy in Pregnancy

- Medications with a narrow therapeutic range:
  - When dosed too high, may cause risks to either the mother or fetus.
  - When under dosed, these medications can be associated with a different set of risks: inadequate treatment.

Overview

- Review the changes in estradiol and progesterone that occur in pregnancy
- Discuss pharmacokinetics in pregnant women using representative medications
  - Heparins: volume of distribution, CO & renal clearance
  - Penicillins: renal clearance & drug transporters
  - Blood flow & protein binding
  - Digoxin: placental drug transporters
  - Phase II Glucuronidation - lamotrigine & labetalol
  - Phase I metabolism – CYP1A2, 3A4, 2D6, 2C9, & 2B6
  - Drug transfer in lactation
Pregnancy: Physiologic Changes

- Hormonal Changes

### Progesterone Production

<table>
<thead>
<tr>
<th>Phase</th>
<th>Site</th>
<th>Production</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular Phase</td>
<td>Ovary</td>
<td>2.5 mg/day</td>
<td>-</td>
</tr>
<tr>
<td>Luteal Phase</td>
<td>Ovary</td>
<td>25 mg/day</td>
<td>30-40 ng/mL</td>
</tr>
<tr>
<td>Term Pregnancy</td>
<td>Placenta</td>
<td>250 mg/day</td>
<td>130-150 ng/mL</td>
</tr>
</tbody>
</table>
Endocrine Changes in Pregnancy

**Estrogens**

- **Pre-pregnancy estradiol**
  - 0.05ng/mL = 50pg/mL

- **Estradiol at term**
  - 25ng/mL = 25,000pg/mL
Pregnancy: Physiologic Changes

- Hormonal Changes
- Fluid Changes = Pregnant women are wetter

Low Molecular Weight Heparins

- Because warfarin crosses the placenta & is a known teratogen, women who require anticoagulation are switched from warfarin to heparins (UFH or LMWH) as soon as or just before she becomes pregnant. Why?
- Molecules > 1000 Daltons do not easily cross the placenta
- Unfractionated heparin chains: 5000 to >40,000 Da
- Even LMWHs are too large
  LMWHs have mass of 3600-9000 Da
Low Molecular Weight Heparins

LMWHs are preferred in pregnancy (vs UFH)
- Longer half-lives
- Decreased dosing frequency
- More predictable anticoagulant effect
- Decreased risk of bleeding
- Decreased need to frequently monitor coagulation parameters
- Reduced risk of heparin-induced thrombocytopenia

Low Molecular Weight Heparins

Anticoagulation in pregnancy
- Estrogen → pregnancy is a hypercoagulable state
- Therapeutic Index for LMWHs is narrow
- LMWHs have to precisely change coagulation

What happens to LMWH pharmacokinetics in pregnancy? How does maternal physiology change how we dose LMWHs?
- Volume of Distribution
- Clearance
Volume of Distribution:
- The Vd of LMWHs = ~ plasma volume
- What happens to LMWH Vd in pregnancy?

Increase in plasma volume:
- About 1200 - 1600 mL above the nonpregnant state, or ~ 40% greater
- Increase begins at 6 - 8 weeks' gestation
- Increase peaks at ~ 32 weeks' gestation
- Increase in plasma volume is related to fetal number: PV increase in triplets is almost double that in singletons
- Increase in RBC volume < blood volume: dilutional anemia
# Body Fluid Spaces in Pregnant and Nonpregnant Women

<table>
<thead>
<tr>
<th>WEIGHT (kg)</th>
<th>PLASMA VOLUME (mL/kg)</th>
<th>ECF SPACE (L/kg)</th>
<th>TBW (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NONPREGNANT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td></td>
<td>0.189</td>
<td>0.516</td>
</tr>
<tr>
<td>70 – 80</td>
<td>49</td>
<td>0.156</td>
<td>0.415</td>
</tr>
<tr>
<td>&gt; 80</td>
<td></td>
<td>0.151</td>
<td>0.389</td>
</tr>
<tr>
<td><strong>PREGNANT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td></td>
<td>0.257</td>
<td>0.572</td>
</tr>
<tr>
<td>70 – 80</td>
<td>67</td>
<td>0.255</td>
<td>0.514</td>
</tr>
<tr>
<td>&gt; 80 (↑37%)</td>
<td></td>
<td>0.240</td>
<td>0.454</td>
</tr>
</tbody>
</table>


## Pregnancy: Physiologic Changes

- **Hormonal Changes**
- **Fluid Changes** = *Pregnant women are wetter*
- **Renal Clearance**
LMWH Clearance in Pregnancy

- LMWH clearance:
  - Hepatic desulfation and depolymerization
  - Renal Clearance

- What happens to LMWH renal clearance in pregnancy?

- GFR is proportionate to cardiac output

- Cardiac output increases by 30 – 50%
  - Increase in CO begins as early as 5 weeks
  - 50% of the increase occurs by 8 weeks
  - CO peaks at about 32 weeks

- CO = Heart Rate x Stroke Volume
  - Both HR and SV increase in pregnancy

- Renal blood flow increases in pregnancy → GFR goes up

GFR during Pregnancy and Postpartum

Low Molecular Weight Heparins

- Based on this knowledge what can we predict will happen to LMWHs in pregnancy?

- Volume of Distribution increases
  - For the same dose, the concentration will be lower in pregnant women

- LMWH renal clearance increases
  - LMWH concentrations and anticoagulant effect may not be sustained for the full dosing interval
  - Therapeutic LMWHs require twice daily dosing

Enoxaparin PK in Pregnancy

- Casele 1999
  13 pregnant women
  Enoxaparin 40 mg sc
  12-15wks, 30-33wks, & 6-8wks PP
  Serial anti-factor Xa activity

- Results:
  - Cmax and trough anti-factor Xa activities were lower in both early & late pregnancy compared to PP (P< 0.05)
  - AUC lower in pregnancy compared to PP (P< 0.05)
  - Tmax – no change
LMWHs in Pregnancy

- Anticipate need to escalate dose

- Barbour 2004 13 pregnancies on therapeutic dalteparin with initial dose 100 IU/Kg BID
  - 85% required one or more upward dose titrations
  - By 30 wks, 50% of women required dalteparin 140 IU/Kg BID to maintain therapeutic anti-Factor Xa levels
  - Trough levels were in the therapeutic range only 9% of the time, despite maintenance of therapeutic peak levels.

Ampicillin Case History

A pregnant woman with a URI caused by ampicillin sensitive *H. influenzae* was treated with oral ampicillin 0.5 gm qid. She failed to respond and an ampicillin level was reported as “undetectable”.

She was cured when ampicillin was given intramuscularly in the same dosage.

*Philipson A. J Inf Dis 1977;136:370-6. (Karolinska Institute)*
### Oral Ampicillin PK in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>AUC IV (cm&lt;sup&gt;2&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>2.2 ± 1.0 *</td>
<td>18.6 ± 5.9 *</td>
</tr>
<tr>
<td>Nonpregnancy</td>
<td>3.7 ± 1.5</td>
<td>28.3 ± 10.2</td>
</tr>
</tbody>
</table>

* P < 0.001


### Cefuroxime in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>V&lt;sub&gt;d&lt;/sub&gt; (L)</th>
<th>Cl(ml/min)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>17.8 ± 1.9</td>
<td>282 ± 34 *</td>
<td>44 ± 5 *</td>
</tr>
<tr>
<td>At Delivery</td>
<td>19.3 ± 3.1</td>
<td>259 ± 35 *</td>
<td>52 ± 10</td>
</tr>
<tr>
<td>Postpartum</td>
<td>16.3 ± 2.1</td>
<td>198 ± 27</td>
<td>58 ± 8</td>
</tr>
</tbody>
</table>

* p < 0.05 in comparison to PP

Amoxicillin in Pregnancy

- **AUC (mcg·hr/mL)**
  - 2\textsuperscript{nd} trim: 15.2 ± 5.6
    - $P = 0.02$
  - 3\textsuperscript{rd} trim: 14.9 ± 2.8
    - $P = 0.003$
  - PP: 20.4 ± 6.6


<table>
<thead>
<tr>
<th></th>
<th>T1/2 (h)</th>
<th>Renal Clearance (L/h/kg) $\approx$ CrCl</th>
<th>Renal Secretion (mL/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2\textsuperscript{nd} trimester</td>
<td>$1.2 \pm 0.5$ ($P=0.05$)</td>
<td>$0.36 \pm 0.11$ ($P&lt;0.001$)</td>
<td>$4.1 \pm 1.7$ ($P=0.002$)</td>
</tr>
<tr>
<td>3\textsuperscript{rd} trimester</td>
<td>$1.3 \pm 0.2$ ($P=0.01$)</td>
<td>$0.31 \pm 0.05$ ($P=0.001$)</td>
<td>$0.31 \pm 0.05$ ($P=0.001$)</td>
</tr>
<tr>
<td>postpartum</td>
<td>$1.6 \pm 0.2$</td>
<td>$0.22 \pm 0.05$</td>
<td>$2.5 \pm 0.8$</td>
</tr>
</tbody>
</table>

- Amoxicillin in pregnancy:
  - Elimination half-lives are shorter
  - Renal clearance is increased
  - Renal secretion is also increased
Renal Net Secretion of Amoxicillin

Renal afferent vessel → Renal Tubule Cell → Urine

- OATP??
- OAT??
- PEPT1
- PEPT2

Organic Anion Transporting Polypeptide
Peptide transporter

Progesterone decreases transcription of PEPT1 by unknown mechanisms (*Watanabe 2006*)

Penicillins in Pregnancy

- **Andrew 2007:**
  Anthrax prophylaxis: after ciprofloxacin, switch to amoxicillin 500 mg po tid; however, trough levels may not be sufficient to adequately treat some strains of Anthrax with higher MICs.

- For most infections, penicillins and cephalosporins are dosed well above the necessary MIC. However, because efficacy requires free drug concentration above the MIC for 60-70% of the dosing interval, prescribing at the upper dosing range and shorter dosing frequency is recommended in pregnancy.
Cephalosporins in Pregnancy

- Cephalosporin Prophylaxis for Cesarean Delivery

  - Elkomy M et al (2014)
  - PK study in 20 women undergoing cesarean section
    - Cefazolin Clearance increased by 74% in pregnancy (CL liters/h, pregnancy 7.18 vs 4.12 post-pregnancy)
    - Cord blood concentration-to-maternal concentration ratio: 0.41 (range, 0.21 to 1.45)
    - Computer simulation showed that the probability of maintaining free cefazolin conc above 8mg/L was <50% in cord blood when <2g or when it was give <1h prior to OR.
    - Recommendations: Cefazolin 2 gm IVPB at 1 h prior to OR

- Cephalosporin Prophylaxis for Cesarean Delivery in Obese Patients

  - Pevzner et al (2011)
  - 29 women undergoing cesarean section
    - BMI categories
      - Lean: BMI <30
      - Overweight: BMI 25 – 29.9
      - Obese: BMI 30 – 39.9
      - Extremely Obese: > 40
    - 2 gm cefazolin IV between 30-60 min prior to incision
    - Sampled:
      - Adipose tissue at beginning & end of CS
      - Myometrium at time of delivery
      - Maternal blood at end of CS
    - Cefazolin theoretic breakpoint for resistance: 4 mcg/g
Cephalosporins in Pregnancy

- Cephalosporin Prophylaxis for Cesarean Delivery in Obese Patients
  - Cefazolin concentration in adipose tissue at skin incision (p<0.001)
    - lean women: 9.4 ± 2.7 mcg/g
    - obese women: 6.4 ± 2.3 mcg/g
    - extremely obese women: 4.4 ± 1.2 mcg/g
  - At incision, 20% of the obese & 33.3% of the extremely obese women had cefazolin adipose concentrations < 4mcg/g
  - At closure, all lean women had therapeutic adipose concentrations; but 20% of the obese & 44.5% of the extremely obese women had cefazolin adipose concentrations < 4mcg/g
  - Conclusion: 2 g cefazolin dose is inadequate in obese women

Cephalosporins in Pregnancy

- Cephalosporin Prophylaxis Guidelines 2013
  - American Society of Health System Pharmacists
  - Infectious Diseases Society of America
  - Surgical Infection Society
  - Society for Healthcare Epidemiology of America

- Recommendations
  - 2 g for women< 120 kg
  - 3 g for women ≥ 120 kg
Pregnancy: Physiologic Changes

- Hormonal Changes
- Fluid Changes = Pregnant women are wetter
- Renal Clearance
- Regional Blood Flow changes

Regional Blood Flow Changes

- Increase in blood flow to uterus - 20% of CO
  - Low resistance arteriovenous shunt
  - Reduces cardiac afterload
- Increase in renal blood flow
- Increase in skin blood flow
- Increase in mammary blood flow
- Decrease in skeletal muscle blood flow
- Decrease in splanchnic blood flow
- Mixed results: hepatic blood flow changes
  - Hepatic metabolism for some medications is dependent on blood flow through the liver
Hepatic Blood Flow in Pregnancy

Although % CO to liver changes, the absolute blood flow remains the same

Robson SC 1990

Pregnancy: Physiologic Changes

- Hormonal Changes
- Fluid Changes = Pregnant women are wetter
- Renal Clearance
- Regional Blood Flow changes
- Changes in Protein Binding
Protein Binding

Why is protein binding important?

- Drug molecules bound to plasma proteins cannot leave plasma and cannot exert drug effect
- Only the free fraction can:
  - Move in and out of the blood stream
  - Exert drug effect
  - Move into the liver and be metabolized or move through the kidney and be excreted
- Drug Assays can either measure total drug (free and bound) or free fraction (measuring free fraction is more expensive)

What happens to Protein Binding in Pregnancy?

Albumin In Pregnancy

What happens to albumin concentration in pregnancy?

P = total protein  A = albumin  * p < 0.05 compared with PP
Plasma Proteins in Pregnancy

- Mean Albumin concentrations
  - 2nd Trimester: 3.6 gm/dL
  - Nonpregnant: 4.2 gm/dL
  - Albumin concentrations continue to decrease during the 2nd trimester until term when they are 70-80% of normal values. (Dean M, et al 1980)

- Minimal change in total protein (except in pre-eclampsia, nephrotic syndrome)

- α₁-acid glycoprotein
  - Binds to basic drugs, while albumin binds acidic and neutral drugs
  - 52% lower at 30-36 weeks vs postpartum (Bardy 1991)

Impact of Protein Binding: Free and Total Phenytoin Levels

- Total drug decreases but because protein binding also decreases, free drug does not change
- Total drug doesn’t change, but if protein binding decreases from 95% to 90%, then free fraction may double

Drugs with narrow therapeutic indices that are highly protein bound: Monitor free fraction, NOT total drug
Drug Transporters

- Transmembrane proteins: facilitate movement of drug across the membrane – either into or out of the cell
- More than 400 in the human genome
- Critically important in moving drug across epithelial surfaces, e.g., intestines, liver, kidney, blood-brain barrier, placenta
- Some require ATP, others don’t
Drug Transporters

- Digoxin
  - Placental transporters
  - Renal transporters

Digoxin in Pregnancy

- Fetal tachyarrhythmias occur in ~ 0.5% of pregnancies
Digoxin in Pregnancy

- If untreated and present for an extended period, fetal SVT can lead to fetal cardiac failure, hydrops, and fetal or neonatal demise.

- Digoxin is the primary initial therapy
  - Slows AV transmission and decreases ventricular rate

- Treating the mom with goal of treating the infant.

Digoxin in Pregnancy

- Very difficult to get therapeutic levels of digoxin in the fetus
  - Umbilical cord digoxin 0.4 ng/mL vs maternal digoxin 3.6 ng/mL
    \((King\ 1984)\)
  - Fetal (umbilical cord) / Maternal levels: 0.1 to 0.9 with ratios frequently < 0.5
    \((Syme\ 2004)\)

- Why are fetal levels so disproportionately low?
Initially when it was discovered that the placenta was rich in CYP enzymes, it was presumed that they were there to protect the fetus by metabolizing potential maternal drug exposure.

Subsequently learned that the vast majority of the CYP 450 enzymes present are involved in placental steroid production.

Drug metabolizing CYPs (families 1, 2 & 4) are only minimally present.

Therefore: Digoxin is NOT being metabolized by the placenta.

However, there are multiple drug efflux and influx transporters that play critical roles in moving molecules in to or away from the fetus.

**P-glycoprotein (Pgp)**

- MDR1 gene (multi-drug resistance)
- ATP binding cassette transporter – efflux transporter
- Transports chemicals back “out” to the other side
- Binds to a large number of different drugs including digoxin
- Location: intestinal mucosa, liver, kidney, blood-brain barrier, PLACENTA: apical brush border – maternal facing
- Two-fold decline in expression between late first trimester and term
**Placental Transport Systems**

- **Maternal Circulation**
  - P-glycoprotein (Pgp)
  - Breast Cancer Resistance Protein (BCRP)
  - Multidrug resistance-associated proteins (MRP-2 & MRP-3)
  - Organic cation transporter (OCT)
  - Serotonin transporter (SERT)
  - Noradrenalin transporter (NET)
  - Organic anion transporting peptide (OATP)
  - Organic cation transporter (OCT)

- **Fetal Circulation**
  - Multidrug resistance-associated proteins (MRP-1, MRP-3, MRP-5)
  - Multidrug resistance protein (MDR-3)
  - Organic cation transporters
  - Organic anion transporters
  - Organic cation transporters

**Maternal Digoxin in Pregnancy**

- 28-32 weeks vs 6-10 weeks postpartum
  - Digoxin 0.25 mg po  (*Hebert, M 2008*)
  - \( \text{AUC}_{0-48} \): 7.3 ± 1.6 vs 9.3 ± 2.2 ng*h/mL  \( P<0.006 \)
    - 19% lower in pregnancy
  - \( \text{Cl}_{\text{renal}} \): 181 ± 25 vs 115 ± 25 mL/min  \( P<0.002 \)
    - 60% greater in pregnancy
    - Good correlation between CrCl and digoxin renal clearance (\( r=0.8 \))
  - \( \text{Cl}_{\text{secretion}} \): 73 ± 22 vs 37 ± 14 mL/min  \( P<0.002 \)
    - 120% greater in pregnancy
  - \( f_u \): 67 ± 4 vs 63 ± 5 %  \( P<0.002 \)
    - 5.8% greater in pregnancy
Renal Secretion of Digoxin

Renal afferent vessel → Renal Tubule Cell → Urine

- OATP
- Pgp

Organic Anion Transporting Polypeptide

Digoxin in Pregnancy

- Digoxin dosing in pregnancy pearls:
  - Don’t be surprised by the high dosing requirements in pregnancy: usually greater than non-pregnant expectations for both maternal and fetal indications
  - Mom can become dig-toxic trying to get adequate fetal levels
  - May need to either directly treat the fetus with digoxin intramuscularly into the fetal thigh or intracadially (increased fetal risk) or add second drug: flecainide, sotalol, amiodarone
Phase II Hepatic Metabolism

- **Glucuronidation**
  Representative medications:
  - Lamotrigine
  - Labetalol

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**Lamotrigine**

- Lamotrigine (LTG) approved mid 1990s for:
  - Partial & absence seizures
  - Primary generalized seizures
  - Mood stabilizer: bipolar disorders
Lamotrigine

- **Tomson 1997** Karolinska Institute
  Plasma LTG decreased as pregnancy progressed:
  Dose / plasma conc compared to 5 mo postpartum:
  3.6 times higher 3rd trimester
  5.8 times higher at delivery
  Suggesting enhanced clearance of LTG during pregnancy

- Lamotrigine levels similarly affected by birth control pills
  LTG levels can be reduced by >50%

- **Sabers 2003**:  
  Mean steady state lamotrigine plasma concentration:
  30 women not on COC: 28 µmol/L
  22 women on COC: 13 µmol/L  \( p < 0.0001 \)

- **Reimers 2005**:  
  LTG concentrations w/ identical LTG doses (mean \pm\ SD)
  COC: combined oral contraception  POP: progestin-only pills
  LTG controls: 5.6 \pm\ 3.1 mg/L
  LTG POP: 5.4 \pm\ 2.1 mg/L
  LTG COC: 2.0 \pm\ 1.3 mg/L  \( p < 0.001 \)
Lamotrigine

- How does estradiol affect lamotrigine clearance?
- How is lamotrigine cleared?

- Phase II hepatic metabolism
  Conjugated via N-glucuronidation followed by renal clearance

Overview of Drug Metabolism

- Phase I and Phase II Hepatic Metabolism

  - Phase I: Conversion into potentially less toxic metabolites
  - Phase II: Addition of moieties that make the drug more water soluble to facilitate renal clearance: sugars, sulfates, amino acids
Phase II Hepatic Metabolism

- Multiple conjugation reactions
  - Glucuronidation – major pathway
    - O-, N-, and S-
  - Sulfation
  - Acetylation
  - Methylation
  - Amino acid conjugation – glycine, taurine, glutathione
- Some drugs conjugated by multiple different enzymes
- UGT: uridine 5’-diphosphate glucuronosyltransferase
  - UGT – 2 subfamilies, 2 chromosomes with at least 20 isoforms
- Lamotrigine glucuronidated primarily by UGT1A4 with some UGT1A3 and possibly a minor role from UGT2B7

Estradiol & Glucuronidation

- Estradiol is a potent inducer of glucuronidation
  - UGT 1A family
    - 1A4 and to a lesser extent 1A3
  - Chen 2009: Estradiol upregulates mRNA UGT1A4
- Estrogens increase clearance of LTG via induction of UGT 1A4
**Lamotrigine**

- **How quickly does the estradiol effect go away?**

  - **Sidhu 2006**
    16 women, 2 COC cycles with & without LTG 300 mg qd

    Trough LTG on 3rd, 5th & 7th days of placebo
    
    - d 3 27%
    - d 5 63%
    - d 7 116%

    LTG levels higher compared to when on COCS

  - Because induction of UGT1A4 by EE quickly falls, women can become lamotrigine-toxic by end placebo week

  - After delivery lamotrigine levels will rise as glucuronidation returns to normal

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**Lamotrigine in Pregnancy**

**Polepally 2014**  
\[ CL/F = \text{DoseRate} / \text{Conc} \]

- 60 women
- 64 pregnancies
- 77% LTG bid
- Epilepsy & Bipolar
- Population-based, nonlinear, mixed-effects model
Lamotrigine in Pregnancy

- Polepally 2014
- Two subpopulations of women with different rates of increases in LTG CL/F during pregnancy: 10-fold difference
- LTG CL/F
  - 77% of women: increases from 2.16 L/h to 6.88 L/h (219%)
  - 23% of women: increases from 2.16 L/h to only 2.62 L/h (21.3%)
- The latter group may not require increases in LTG at all
- NO correlation w/ weight, age, race, disorder
- Mechanism not known:
  - Polymorphisms in UGT1A4?
  - Differences in UGT1A4 upregulation by E2?
  - 2nd group: maybe glucuronidation doesn’t change at all & the difference in CL/F is from renal changes only?

Labetalol in Pregnancy

- Some labetalol facts:
  - Vd not particularly changed in pregnancy
  - Elimination
    Phase II metabolism via glucuronidation predominantly UGT1A1 & UGT2B7 to inactive metabolites, then renally cleared

What happens to UGT1A1 & UGT2B7 in pregnancy?
Labetalol in Pregnancy

- Rogers, Sibai & Whybrew 1990
  - 8 women, PK study in the 3rd trimester
  - Labetalol elimination half-life shorter in pregnancy:
    - Pregnancy: 1.7 h
    - Historic nonpregnant controls: 6 – 8 h

Labetalol PK in Pregnancy

- Fischer 2014
  - 57 women with cHTN on labetalol
  - 12 weeks gestation until 12 weeks postpartum
  - 649 samples
  - Sparse sampling, Population PK analysis

- Results:
  - Labetalol apparent oral clearance (CL/F)
    - CL/F at 12 weeks gestation: 1.4 fold greater than PP
    - CL/F at 40 weeks gestation: 1.6 fold greater than PP
Upregulation of UGT1A1

- **Jeong 2008**
- Cultured hepatic cells HepG2
- Among possible UGTs, UGT1A1 & 2B7 identified as those primarily responsible for labetalol metabolism
- Effects of estradiol, estrone, estriol & progesterone on upregulation of PXR (intermediary receptor that upregulates transcription of UGT1A1) analyzed
- **Progesterone** NOT estrogen induces UGT1A1 transcription, concentration dependent
- Promotor of UGT2B7 not affected by any tested hormone
- Different UGT enzymes appear to be induced by different mechanisms

Labetalol in Pregnancy

- **Recommendations:**
  - Dose to control BP
  - Monitor trough BPs to ensure BP control throughout dosing interval
  - Dosing interval may need to be shortened from q 12h to 8h
Overview of Drug Metabolism

• Phase I and Phase II Hepatic Metabolism

Phase I = chemical modification
Phase II = biotransformation

Phase I: Conversion into potentially less toxic metabolites
oxidation, reduction, hydroxylation, cyclization & decyclization

Phase II: Addition of moieties that make the drug more water soluble to facilitate renal clearance: sugars, sulfates, amino acids

Cytochrome P450 enzymes

• 12 Families – based on amino acid homology
• Drug metabolism - CYP 1, 2 & 3 families
• Subfamilies A, B, C – based on homology with an additional number if more than one subfamily
  1A1 & 1A2, 2C9 & 2C19, 3A4 & 5, 3A7 (fetal)
• Redundancy:
  • More than one enzyme catalyzes same reaction
  • Some drugs are metabolized by one enzyme
  • Some drugs metabolized by multiple enzymes
• Pregnancy can affect the various CYP enzymes differently
### CYP Activity in Pregnancy

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Change in Pregnancy</th>
<th>Medications Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>increased</td>
<td>midazolam</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>varies</td>
<td>dextromethorphan</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>decreased</td>
<td>caffeine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>increased</td>
<td>glyburide</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>decreased</td>
<td>proguanil</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>increased</td>
<td>methadone</td>
</tr>
</tbody>
</table>

### Phase I Metabolism & Pregnancy

- **Tracy 2005**
  3 stages of pregnancy (14-18wks, 24-28wks, 36-40 wks) vs 6-8 wks postpartum
  - probe medications for specific CYP activity
  - CYP1A2: salivary caffeine clearance:
  - CYP2D6: dextromethorphan O-demethylation
  - CYP3A: dextromethorphan N-demethylation

- **CYP1A2**: progressively decreases across pregnancy
  - -32.8% +/- 22.8%, -48.1% +/- 27%, -65.2% +/- 15.3%

- **CYP2D6**: increases sequentially across pregnancy
  - 25.6% +/- 58.3%, 34.8% +/- 41.4%, 47.8% +/- 24.7%
  - Excluded from analysis: CYP2D6 poor metabolizers

- **CYP3A**: increased at all pregnancy stages by 35-38%
Caffeine Clearance during Pregnancy and Postpartum

CYP1A2 activity: theophylline, ropivacaine, lidocaine, ondansetron, olanzapine, clozapine


CYP3A

- CYP3A family: metabolizes more than 50% of medications
  - eg:
    - alprazolam, amiodarone, amlodipine, amprenavir, buspirone, carbamazepine, cisapride, citalopram, cyclosporine, diltiazem, efavirenz, erythromycin, estrogens, felodipine, fentanyl, fluconazole, indinavir, itraconazole, ketoconazole, lidocaine, loratidine, methadone, metronidazole, midazolam, nelfinavir, nicardipine, nifedipine, omeprazole, phenobarbital, prednisolone, progesterone, quetiapine, rifampin, sirolimus, statins, tacrolimus, testosterone, trazadone, R-warfarin, zolpidem
CYP3A Activity in Pregnancy

- **Hebert MF 2008**
  Midazolam (probe marker for CYP3A activity)
  3rd trimester vs 6-10 wks postpartum
  - 1’OH-mid Cl\textsubscript{formation} increases by 124±63\% (P=0.002)
  - AUC decreases by 46±26\% (P=<0.002)
  - C\textsubscript{max} decreases by 28±32\% (P=0.01)
  - Apparent oral Cl increases by 108±62\% (P=0.002)

---

CYP3A & Midazolam

![Average midazolam plasma concentration–time profiles](image)

*Hebert MF 2008*
CYP3A Activity in Pregnancy

- **Indinavir**
  - Protease inhibitor, anti-retroviral therapy
  - Metabolized by CYP3A4/5
- **Unadkat JD 2007**
  - 16 HIV+ pregnant women 14 - 28 wks’ gestation INV PK
  - Compared to same women 12 wks postpartum
  - Indinavir 800 mg tid (+ zidovudine & lamivudine)
- Mean AUC: approximately 3-fold lower in pregnancy

CYP3A Activity in Pregnancy

- Indinavir mean AUC pregnancy vs postpartum

*Unadkat JD 2007*
Nifedipine

- Nifedipine
  - Extended release formulation: chronic hypertension
  - Immediate release formulation: tocolysis

Nifedipine in Pregnancy

- Prevost (Sabai) 1992
  - 15 women w HTN, 3rd trimester
  - Nifedipine 10 mg dose q 6h (capsules)
  - PK study at steady state after 48h
  - Compared to historic controls

- $C_{\text{max}}$ decreased: $38.6 \pm 18$ vs $73.48 \pm 17.48$ ng/mL
- $t_{1/2}$ decreased: $1.3 \pm 0.5$ vs $3.43 \pm 10.6$ h
- Clearance increased: $2.0 \pm 0.8$ vs $0.49 \pm 0.09$ L/hr/kg
- Undetected levels at 360 min (6 h)
- Recommendation: decrease dosing frequency to q 4 h
- This and several other studies showed wide variation in nifedipine concentrations with the same dose. Why?
Haas 2013
14 women undergoing tocolysis
Steady state dosing of 10-20 mg q 4 - 8h
q 4h: 1; q 6h: 12; q 8h: 1
PK analysis of nifedipine & metabolite - normalized
blood: trough, 0.5, 1, 1.5, 2, 3, 4, 6 & 8h post-dose

CYP3A4: 5 – 20 fold more efficient at metabolizing nifedipine
in pregnancy compared to historic controls

Haas 2013
Genotyping: CYP3A5 *1 (active allele), *3, *6, *7
CYP3A4*1B (promotor SNP w/ ↑ activity)

Active CYP3A5*1 expressed in:
  Caucasians: 10 – 20%
  African-Americans: 75%

CYP3A4*1B & CYP3A5*1 are linked – located close to each
other on chromosome 7 – inherited together
**Nifedipine in Pregnancy**

*Haas 2013* Results:

4/14 women were high expressers of *CYP3A5*1 (increased activity) of these, 1 was homozygous for *CYP3A4*1B (increased activity) & 2 were heterozygous for *CYP3A4*1B.

No other women carried *CYP3A4*1B

Effect of *CYP3A* genotype on oral clearance of nifedipine:

- Women with wild-type *CYP3A5*1 had increased nifedipine oral clearance
- *CYP3A4*1B allele carriers: open circles
- non-*CYP3A4*1B carriers: dark circles

Women w both *CYP3A5*1 & *CYP3A4*1B have enhanced clearance of nifedipine

<table>
<thead>
<tr>
<th>Historic controls</th>
<th>CYP3A5 high expressers (n=3)</th>
<th>CYP3A5 low expressers (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (μg/L)</strong></td>
<td>102 ± 56.5 (60.8–184)</td>
<td>190 ± 121 (40.6–397)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;ave&lt;/sub&gt; (μg/L)</strong></td>
<td>14.7 ± 2.5 (12.2–18.2)</td>
<td>51.8 ± 30.8 (20.3–119)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</strong></td>
<td>&gt;2–3.4 (0.98–2.35)</td>
<td>1.7 ± 1.8 (0.8–6.9)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Cl/F (L/h)</strong></td>
<td>35–38 L/h</td>
<td>232 ± 37.8 (183–275)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>85.6 ± 45.0 (39.1–164)</td>
<td>0.000095</td>
</tr>
</tbody>
</table>
If 75% of African-Americans carry the CYP3A5*1 & CYP3A4*1B combination – are their nifedipine levels lower? Are they less responsive to nifedipine tocolysis?

CYP2D6

CYP2D6: 2nd most active CYP enzyme ~20% of drugs
eg:
Amitriptyline, clomipramine, codeine, dextromethorphan, doxepin, flecaïnide, fluoxetine, fluvoxamine, haloperidol, hydrocodone, imipramine, metoprolol, nortriptyline, paroxetine, promethazine, propranolol, risperidone, venlafaxine, tamoxifen
CYP2D6 Genotype & Phenotype

<table>
<thead>
<tr>
<th>Metabolic Phenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor metabolizer</td>
<td>No functional gene</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>One active gene</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Two active genes (&quot;normal&quot;)</td>
</tr>
<tr>
<td>Ultra Rapid metabolizer</td>
<td>Multiple copies of an active gene</td>
</tr>
</tbody>
</table>

- Genetically determined polymorphisms
- Activity can vary 1000-fold
- Ethnic differences in allelic prevalence
  - Poor metabolizers: 5-10% of Caucasians
    Uncommon in Africans, Asians & South Americans
  - Ultra Rapid Metabolizers: 10-50% East Africans, Arabians & Pacific Islanders
    1-5% of Caucasians

Dextromethorphan Metabolism

Dextromethorphan metabolism involves both CYP2D6 & 3A4 to final metabolite, 3-hydroxymorphinan

CYP2D6: O-demethylation
CYP3A4: N-demethylation

To isolate CYP2D6 activity, evaluate ratio of dextromethorphan to dextrorphan concentrations
CYP2D6 Genotype & Phenotype

- Dextromethorphan / Dextrorphan Ratio
- Not thought to be a classically inducible enzyme

Trojan A, Breast Care 2012

Dextromethorphan CYP2D6

- CYP2D6: dextromethorphan O-demethylation
  - Wadelius M 1997
  - 17 pregnant women phenotyped for CYP2D6 & 7-11 weeks postpartum
  - 4 poor, 7 heterozygous extensive & 6 extensive
  - Dextromethorphan/dextrorphan metabolic ratio

- Ratio significantly reduced = increased CYP2D6 activity:
  - Homozygous & heterozygous extensive metabolizers
    mean decrease 53% (P=0.0015)

- Ratio increased in poor metabolizers = decreased activity
  - Homozygous poor metabolizers
    mean increase 63% (P not calculated in 4 subjects)
CYP2C9

- CYP2C9 – metabolizes about 10% drugs
  - Eg:
    - Amitriptyline, celecoxib, diclofenac, flubiprofen, fluoxetine, fluvastatin, glipizide, glyburide, ibuprofen, losartan, meloxicam, naproxen, omeprazole, phenytoin, piroxicam, sulfamethoxazole, tamoxifen, tolbutamide, torsemide, valproic acid, voriconazole, S-warfarin

Glyburide
- Predominantly metabolized by CYP2C9 with some contribution from CYP3A4 & CYP2C19
- Hebert MF 2009
  - Glyburide concentrations 50% of non-pregnant at same dose
  - Gestational increase in apparent oral clearance of free glyburide
  - Gestational increase of formation clearance of OH-metabolite >2X
  - Anticipate need for higher doses of glyburide in pregnancy

Pharmacokinetics in Pregnancy

- Net effect of pregnancy changes not always predictable

- \[ t_{1/2} = \ln(2) \cdot \frac{V_d}{Cl} \]
  - If both clearance and \( V_d \) increase, elimination half-life may stay the same or be minimally affected

- Drugs metabolized by multiple enzymes: if activity of one pathway is decreased, dominance may shift to an alternate pathway, decreasing the influence of the primary change

- Significant interpersonal variability in response to induction stimulants.
Pharmacokinetics in Pregnancy

- Changes in Vd, GFR, protein binding reflect normal pregnancy physiology, but why do changes occur in hepatic metabolism, renal secretion or other transporters?

- One hypothesis – classic enzyme induction:
  - Xenobiotic Sensing Receptors – Nuclear Receptors
    - Pregnane X-receptor (PXR)
    - Constitutive androstan receptor (CAR)

- Early Vertebrates: PXR regulates bile acid metabolism
  - evolved from an early estrogen steroid nuclear receptor
  - pre-mammalian development doubled: PXR & CAR

Xenobiotic Inducing Enzymes & Transporters

- In mammals – PXR LBD evolved to protect the organism from xenobiotics which could disrupt its endogenous steroid equilibrium (ensures reproduction)

- Up regulates transport and metabolism proteins that keep toxic chemicals out and get rid of what does get in. Mechanisms to detoxify xenobiotics also transport and metabolize modern drugs.

- Drug binds to PXR and/or CAR
  Activated PXR or CAR complexes form a heterodimer with the Retinoid X Receptor (RXR) which binds to the regulatory region of specific enzymes and transporters.

Hypericum – St John’s wort

Digitalis – Fox Glove
Orphan Nuclear Receptors

Xenobiotic Inducing Enzymes & Transporters

Representative genes controlled by PXR & CAR
Overlap of both genes upregulated as well as drugs that bind to them

- **PXR**
  - CYP 1A1, 1A2 ?
  - CYP 2A6, 2B6
  - CYP 2C8, 2C9, 2C19
  - CYP 3A4, 3A7
  - CYP 24A (Vit D)
  - SULT 2A1
  - UGT 1A1, 1A3, 1A4
  - Glutathione S-transferase
  - MDR1 (Pgp)
  - MRP2 & 3
  - AHR1
  - OATP2

- **CAR**
  - CYP 1A1, 1A2 ?
  - CYP 2A6, 2B6
  - CYP 2C8, 2C9, 2C19
  - CYP 3A4, 3A7
  - CYP 24A (Vit D)
  - SULT 2A1
  - UGT 1A1, 1A3, 1A4
  - Glutathione S-transferase
  - Amino-N-SULT
  - PAPS
  - MRP1, MRP2 & 3
  - AHR1
Enzyme Inducing Drugs

- Some Drugs that bind to PXR and/or CAR
  - Rifampin
  - Mifepristone (RU 486)
  - Estrogen (but not ethinyl estradiol)
  - Progesterone & other progestins
  - Phenobarbital, carbamazepine, phenytoin, oxcarbazepine
  - Calcium channel blockers
  - Cortisol, prednisolone
  - St. John’s Wort - hyperforin
  - Protease inhibitors
  - Statins

- What up-regulates PXR/CAR in pregnancy?
- Why are some CYPs down-regulated in pregnancy?

Drugs and Lactation

- Mechanisms of drug transfer
  - Diffusion
  - Intercellular movement
  - Active transporter

- Drugs with poor bioavailability, even if present in breast milk, achieve low infant levels due to poor oral absorption

- Most drugs are safe to use with lactation
- Specific Drug Examples
Factors that affect drug transfer into the alveolar lumen

Passive Diffusion – dominant mode
- Molecular size
- Degree of ionization
- Lipid solubility
- Protein binding
- Drugs that are most readily transferred:
  - low molecular weight
  - no ionization (no electrical charge)
  - highly lipid soluble
  - low protein binding

Drug Transfer into Breastmilk
- Transcellular diffusion
  - Small molecules <200-300 daltons readily diffuse across into breast milk
- Influenced by differences in:
  - pH (6.8–7.2 for milk vs. 7.4 for plasma)
  - lipids (3% for milk vs. 1% for plasma)
  - protein (1% for milk vs. 8% for plasma)
- Intercellular (paracellular) mechanism used for larger molecules, eg: maternal antibodies or monoclonal antibody drugs
- All but a few drugs transfer via simple or facilitated diffusion
Drugs Exposure with Lactation

General Rules

- Milk concentrations are usually lower than maternal plasma concentrations.
- There usually is a fixed ratio between milk and plasma concentrations.

Kinetic Analysis of Theophylline: Plasma and Milk Concentrations

---

Three methods of expressing Infant drug exposure:
- Milk to Plasma Drug concentration ratios
- Relative Infant Drug
- Plasma drug concentration in the infant
Milk to Maternal Plasma Drug Concentrations

Milk to Maternal Plasma Drug Concentrations  M:P Ratio

- **Drug concentration in breast milk**
- Drug concentration in maternal plasma
- Most commonly used method to assess drug transfer
- Does not express other factors that can affect drug exposure:
  - How much milk/drug is infant actually getting per day
  - How much drug is being absorbed
  - How well does the infant metabolize the drug

Relative Infant Dose

- Estimation of infant drug exposure per day as a percentage of the dose to the mother:
  \[
  \text{Relative Infant Dose} = \frac{\text{dose to infant/day}}{\text{dose to mother/day}} \quad (\text{mg/kg/day})
  \]
- Dose to infant is based on measurement drug concentration in breast milk & maternal and total milk volume ingested per day,
  Milk volume estimate: 150 mL/Kg/day
  \[
  \text{Infant dose/day} = C_{\text{mat}} \times M/P \times V_{\text{milk}}
  \]
- RID < 10% is considered relatively safe but also need to factor in medication risks
Breast Cancer Resistance Protein

- ATP efflux transporter
- Apical border of mammary cells
- Transports drug against a concentration gradient into milk
- Expressed with lactation, PRL induced
- Produces increased M/P ratios
- Unclear primary function
- No other ATP transporters present

BRCP & Elevated M/P Ratios

<table>
<thead>
<tr>
<th>Medication</th>
<th>M/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>5.1</td>
</tr>
<tr>
<td>Bupropion</td>
<td>2.5 – 8.6</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>29.3</td>
</tr>
<tr>
<td>∆-9-THC</td>
<td>8</td>
</tr>
<tr>
<td>Diazepam</td>
<td>3.7 – 9.5</td>
</tr>
<tr>
<td>Nadolol</td>
<td>4.6</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>31.1</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>13</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>4.9</td>
</tr>
<tr>
<td>Tepotecan</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Nitrofurantoin Safety
- Even with M/P ratio of 31.1, nitrofurantoin is considered safe in lactation (in G6PD negative infants) because fetal dose remains small: Gerk 2001 estimated that a breastfed infant would only consume 0.2 mg/kg (6% of the maternal dosage) of nitrofurantoin each day.

Plasma drug concentration in the infant
- Drug delivery from milk
- Oral bioavailability in the infant
- Drug clearance in the infant
Drug Transfer during Lactation

- Drugs generally contraindicated during lactation
  - Antineoplastics
  - Immune suppressants
  - Ergot Alkaloids
  - Gold
  - Iodine
  - Lithium carbonate
  - Radiopharmaceuticals
  - Social drugs / drugs of abuse